(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 128 007**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 84303644.3

(22) Date of filing: 31.05.84

(51) Int. Cl.³: C 07 D 295/12
C 07 D 295/10, C 07 D 295/18
//A61K31/495

(30) Priority: 02.06.83 JP 98713/83

(43) Date of publication of application:
12.12.84 Bulletin 84/50

(84) Designated Contracting States:
CH DE FR GB IT LI

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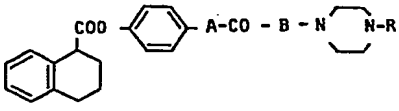
(54) Phenyl tetrahydronaphthylcarboxylate derivatives.

(57) Phenyl tetrahydronaphthylcarboxylate derivatives of the formula (I) and acid addition salts thereof:



(I)

wherein A is a direct bond, or a lower alkylene, vinylene or imino group; B is a direct bond, a lower alkylene or –NH–lower alkylene group, or an –OCH_2CO– residual group; and R is a lower alkyl group, with the proviso that A and B are not both direct bonds, and A, B and R are not a lower alkylene group, a direct bond and a methyl group, respectively, at the same time, are effectively useful as chymotrypsin inhibitors.

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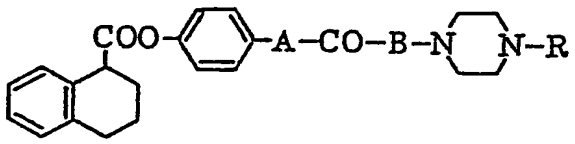
"PHENYL TETRAHYDRONAPHTHYLCARBOXYLATE DERIVATIVES"

This invention relates to novel phenyl tetrahydronaphthylcarboxylate derivatives, and more specifically to phenyl tetrahydronaphthylcarboxylate derivatives represented by the following formula (I); and their acid addition salts:-



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wherein A is a direct bond, or a lower alkylene, vinylene or imino group; B is a direct bond, a lower alkylene or -NH-lower alkylene group, or an $-OCH_2CO-$ residual group; and R is a lower alkyl group, with the proviso that A and B are not both direct bonds, and A, B and R are not a lower alkylene group, a direct bond and a methyl group, respectively, at the same time.

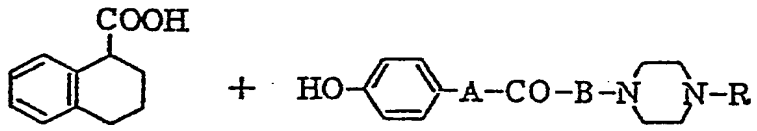
Numerous phenyl esters have been previously found by the present inventors which can exert remarkable chymotrypsin inhibitory effects (Japanese Patent Laid-open Publication No. 38243/1983).

The present inventors have further synthesized a series of compounds analogous to such phenyl esters and have determined their physiological activities. Through these research efforts leading to this invention, it has been discovered that phenyl tetrahydronaphthylcarboxylates

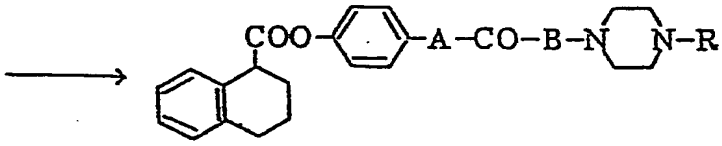
of the formula (I) above and their acid addition salts have more excellent inhibitory effects on chymotrypsin.

The compounds of the formula (I) and their acid addition salts, are useful by virtue of their chymotrypsin inhibitory characteristics for various purposes, for example, as drugs for the therapy of pancreatic diseases.

Compounds of the formula (I) according to this invention can be prepared, for example, by esterifying tetrahydronaphthylcarboxylic acids of the formula (II) below with 4-substituted phenols of the formula (III) below in accordance with the following reaction scheme:



(II) (III)



(I)

wherein the symbols A, B and R have the same meanings and restrictions, as defined

above.

The esterification reaction referred to above may be carried out by methods commonly employed in the art. One suitable method useful in the invention is to react reactive derivatives of the compounds of the formula (II), such as their acid halides, acid anhydrides, mixed acid anhydrides, active esters, azides and the like, with the compounds of the formula (III). Another advantageous method involves reacting the compounds of the formula (II) with the compounds of the formula (III) in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, or the like.

Where it is found desirable, the thus obtained compounds of the formula (I) may be converted in conventional manner to inorganic or organic acid addition salts thereof. Eligible inorganic acids include, for example, hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and like acids. Eligible organic acids include, for example, acetic acid, propionic acid, maleic acid, fumaric acid, tartaric acid, oxalic acid, citric acid, methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, and like acids.

Some selected compounds of this invention were tested with respect to their chymotrypsin inhibitory effects.

The tests were conducted in accordance with the procedure of Muramatsu et al [The Journal of Biochemistry, 62, 408 (1967)]. A mixture was prepared which was made up

of 0.1 mℓ of a dimethylsulfoxide solution of each test compound, 0.1 mℓ of water and 0.1 mℓ of a buffer solution containing 10 μg/mℓ of chymotrypsin (0.1M Tris-HCℓ buffer, pH 8.0). The mixture was incubated for 10 minutes, followed by addition of 0.2 mℓ of a buffer solution containing 25 mM of an ethyl ester of acetyl-L-tyrosine. The resulting mixture was reacted at 37°C for 30 minutes. The remaining substrate was caused to develop a color by the Hesterin method, whereupon its absorbance was measured at 530 nm. As a comparative compound, use was made of tosylphenylalanine chloromethyl ketone (TPCK) which is known as an inhibitor for chymotrypsin.

The results are shown in Table 1 in which the numbers of the test compounds are indicated as those of the corresponding examples given hereunder.

Table 1

Test Compound	Inhibitory Activity [50% Inhibitory Concentration (M)]
1	4×10^{-6}
2	3×10^{-6}
3	7×10^{-7}
4	6×10^{-7}
5	3×10^{-8}
Comparative compound (TPCK)	5×10^{-4}

This invention is illustrated by the following non-limitative examples:-

Example 1

1-Isopropyl-4-[{4-(1,2,3,4-tetrahydro-1-naphthoyloxy)-phenyl} carbamoylmethyl]piperazine.dihydrochloride

1) One hundred milliliters of an ethanol solution containing 7 g of 1-isopropylpiperazine, 6.2 g of ethyl chloroacetate and 9.2 m of triethylamine was heated and refluxed for 4 hours. After being concentrated under reduced pressure, to the resulting mixture was added ethyl acetate. Insoluble matter was removed by filtration. Thereafter, the residue was purified by silica gel chromatography (eluent: a 20:1 mixture of chloroform and methanol) to obtain 7.4 g of 1-ethoxycarbonylmethyl-4-isopropylpiperazine as a light brownish oily substance.

The oily substance thus obtained was dissolved in a solvent consisting of 75 mℓ of ethanol and 3.5 mℓ of water, followed by addition of 1.6 g of sodium hydroxide. The mixture was stirred overnight and then neutralized with hydrochloric acid. Insoluble matter was removed by filtration and the residue concentrated under reduced pressure. The resulting oily substance was dissolved in chloroform. The chloroform solution was dried, whereupon the solvent was removed by distillation to obtain 4.76 g of 1-hydroxy-carbonylmethyl-4-issopropylpiperazine as light brownish powder.

To 6 mℓ of a chloroform solution containing 559 mg of

the thus obtained compound, 109 mg of p-aminophenol and 36 mg of 4-dimethylaminopyridine, was added 619 mg of dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 2 hours. After being concentrated under reduced pressure, to the resulting mixture was added 10 mℓ of ethyl acetate. Insoluble matter was removed by filtration, and the residue was extracted with 10 mℓ of 1N HCℓ. After being neutralized with sodium hydrogen carbonate, the mixture was extracted with 20 mℓ of chloroform. The chloroform layer was washed with an aqueous saturated NaCℓ solution and dried, and the solvent was removed by distillation to obtain 410 mg of a light yellowish substance. Thereafter, the substance was dissolved in 3 mℓ of methanol, followed by addition of 1.5 mℓ of an aqueous ammonia solution. The resulting mixture was stirred overnight and then concentrated under reduced pressure to obtain 255 mg of 1-(4-hydroxyphenyl)carbamoylmethyl-1-isopropylpiperazine as a yellowish substance.

2) To 10 mℓ of an ethyl acetate solution containing 684 mg of the 1-(4-hydroxyphenyl)carbamoylmethyl-4-isopropylpiperazine obtained in item 1) above, 650 mg of 1,2,3,4-tetrahydro-1-naphthylcarboxylic acid and 45 mg of dimethylaminopyridine, was added 770 mg of dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 2 hours. Insoluble matter was removed by filtration. The residue was extracted with 10 mℓ of 1N HCℓ and then neutralized with sodium hydrogen carbonate. After

being washed with water and dried, the resulting mixture was concentrated under reduced pressure to obtain a light yellowish substance. The substance was purified by silica gel column chromatography (eluent: a 20:1 mixture of chloroform and methanol) and dissolved in 20 mℓ of ethanol. To the ethanol solution was added hydrochloric acid to obtain 684 mg (yield: 54.6%) of 1-isopropyl-4-[{4-(1,2,3,4-tetrahydro-1-naphthoyloxy)phenyl}carbamoyl-methyl]piperazine dihydrochloride as colorless crystals having a melting point of 235 to 240°C (decomposed).

Examples 2 to 7

The procedures of Example 1 were repeated to obtain six compounds of the formula (I), details of which are tabulated in Table 2.

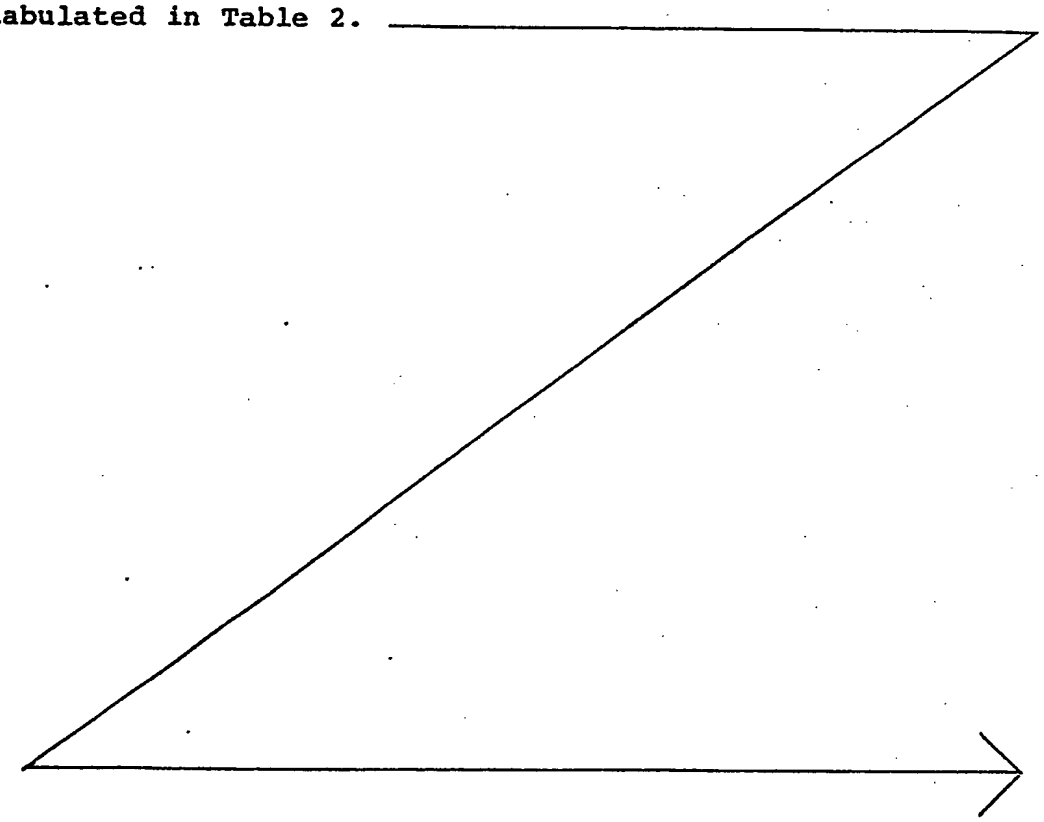
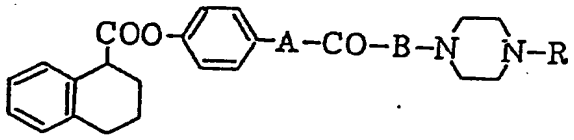


Table 2

Example No.	Compound (I) A	B	R	Salt	Yield (%)	Appearance	Melting Point (°C)
2	-CH=CH-	-	$-CH(CH_3)_2$	HCl	61.5	Colorless crystals	207 - 210
3	-	$-NHCH_2CH_2-$	$-CH(CH_3)_2$	-	38.1	Light yellowish crystals	102 - 103
4	-CH=CH-	-	$-CH_3$	$(COOH)_2$	72.2	Colorless powdery crystals	146 - 150
5	-	$-OCH_2CO-$	$-CH(CH_3)_2$	HCl	56.8	Colorless crystals	196.5 - 198
6	$-CH_2CH_2-$	-	$-CH(CH_3)_2$	HCl	35.8	Colorless needle-like crystals	169 - 171
7	$-CH_2-$	-	$-CH(CH_3)_2$	HCl	56.3	Colorless needle-like crystals	188 - 192

CLAIM

1. Phenyl tetrahydronaphthylcarboxylate derivatives represented by the following formula (I), and pharmaceutically acceptable acid addition salts thereof:-



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B is a direct bond, a lower alkylene or -NH-lower alkylene group, or an $-OCH_2CO-$ residual group; and

R is a lower alkyl group,

with the proviso that A and B are not both direct bonds, and A, B and R are not a lower alkylene group, a direct bond and a methyl group, respectively, at the same time.